

**REMARKS**

Claims 10-14, 16, 18, 19 and 22-27 were pending. Of these pending claims, claims 18, 19 and 22-27 have been withdrawn. Claim 16 has been cancelled hereinabove without prejudice. Claims 10 and 14 have been amended herein. Support for the amendments to claims 10 and 14 may be found, *inter alia*, on pages 2-4 of the PCT publication. No new matter has been added by these amendments. Since applicants believe that these amendments further clarify the distinctions between the cited references and the instant invention discussed in the response to the previous Office Action and since applicants believe these amendments place the application in condition for allowance or places the application in better condition for appeal pursuant to 37 C.F.R. § 1.116, applicants respectfully request that the Examiner accept the amendments and enter them into the instant case.

**Rejections Under 35 U.S.C § 103**

In the Final Office Action the Examiner rejected claims 10-13 and 16 under 35 U.S.C. § 103(a) based on International Patent Application Publication WO 00/66180 (“Balaban”) and Aime et al. (Magnetic Resonance in Medicine, 2002) (“Aime I”) and in further view of Frullano et al. (“Frullano”).

In the Final Office Action the Examiner also rejected claim 14 under 35 U.S.C. § 103(a) based on Balaban, Aime I, and Frullano and further in view of Aime et al. (JACS, 1995) (“Aime II”).

**Independent Claim 10**

Applicants point out that the only currently pending independent claim is claim 10 which now recites:

A method of imaging a subject comprising,

administering to the subject a paramagnetic CEST agent comprising,

a substrate molecule (SH) comprising at least one mobile proton in exchange with bulk water bound by electrostatic interaction having a thermodynamic constant of association  $K_a$  greater than 10 to a paramagnetic chelate complex (SR) of a metal ion selected from the group consisting of:

iron (II) (high-spin configuration), iron (III), cobalt (II), rhodium (II), copper (II), nickel (II), cerium (III), praseodymium (III), neodymium (III), dysprosium (III), erbium (III), terbium (III), holmium (III), thulium (III), ytterbium (III) and europium (III),

applying an rf pulse sufficient to saturate the resonance of the at least one mobile proton shifted from the bulk water as a result of said electrostatic interaction to create a saturated magnetization that is transferred to the bulk water through chemical exchange, and

imaging the subject using a CEST-based MRI procedure.

Applicants point out that none of Balaban, Aime I, and Fullano disclose, teach or suggest alone or in combination any of the following:

1. Methods of imaging a subject using a paramagnetic CEST agent having a substrate molecule (SH) comprising at least one mobile proton in exchange with bulk water bound by electrostatic interaction to a paramagnetic chelate complex.
2. Methods in which the electrostatic interaction referenced above has a thermodynamic constant of association  $K_a$  greater than 10.
3. Methods which include applying an rf pulse sufficient to saturate the resonance of the at least one mobile proton shifted from the bulk water as a result of said electrostatic interaction to create a saturated magnetization that is transferred to the bulk water through chemical exchange.

It is of course black letter law that if even a single element of a claim is not disclosed, taught or suggested by the cited references alone or in some combination, that a 35 U.S.C. § 103(a) rejection cannot stand. In the instant case applicants maintain that there are at least three elements of the independent claim that are not disclosed, taught or suggested by the cited references alone or in any combination. Each of these three elements is fully supported by the specification. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 10 under 35 U.S.C. § 103(a).

Dependent Claims 11-13

Since each of the currently pending independent claims add at least one element to independent claim 10, they are likewise not obvious for the reasons stated above with respect to independent claim 10.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of dependent claims 11-13 under 35 U.S.C. § 103(a).

Dependent Claim 14

The Examiner also rejected dependent claim 14 applying the same references which were applied to independent claim 10 and also applying Aime II.

Applicants note that Aime II does not cure any of the deficiencies of Balaban, Aime I and Frullano with respect to, *inter alia*, the three elements cited above with respect to independent claim 10.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of dependent claim 14 under 35 U.S.C. § 103(a).

**Obviousness-Type Double Patenting Rejections**

In the Final Office Action the Examiner provisionally rejected the pending claims on the ground of non-statutory obviousness-type double patenting based on co-pending U.S. Serial No. 10/502,701. Since this is a provisional rejection based on another co-pending application, applicants respectfully request that this rejection be held in abeyance until the appropriate time.

**Conclusion**

In view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the rejections raised in the Final Office Action and allow each of the presently pending claims, namely claims 10-14.

No fee, other than the fee for a three-month extension of time, is believed to be due in connection with the filing of this Amendment. However, the Director is hereby authorized to charge any additional fee(s) deemed necessary to Deposit Account No. 02-2275.

If a telephone interview would be of assistance in advancing prosecution of this application, Applicants' undersigned attorney respectfully requests that the Examiner telephone him at the number provided below.

Respectfully submitted

Date: February 25, 2011

By: /Robert E. Alderson/  
Robert E. Alderson, Reg. No. 44,500  
LUCAS & MERCANTI, LLP  
475 Park Avenue South  
New York, NY 10016  
Phone: (646) 783-6757  
Fax: (212) 661-8002